

Note to readers with disabilities: *EHP* strives to ensure that all journal content is accessible to all readers. However, some figures and Supplemental Material published in *EHP* articles may not conform to [508 standards](#) due to the complexity of the information being presented. If you need assistance accessing journal content, please contact ehp508@niehs.nih.gov. Our staff will work with you to assess and meet your accessibility needs within 3 working days.

Supplemental Material

Colorectal Cancer and Long-Term Exposure to Trihalomethanes in Drinking Water: A Multicenter Case-Control Study in Spain and Italy

Cristina M. Villanueva, Esther Gracia-Lavedan, Cristina Bosetti, Elena Righi, Antonio José Molina, Vicente Martín, Elena Boldo, Nuria Aragonés, Beatriz Perez-Gomez, Marina Pollan, Ines Gomez Acebo, Jone M. Altzibar, Ana Jiménez Zabala, Eva Ardanaz, Rosana Peiró, Adonina Tardón, Maria Dolores Chirlaque, Alessandra Tavani, Jerry Polesel, Diego Serraino, Federica Pisa, Gemma Castaño-Vinyals, Ana Espinosa, Nadia Espejo-Herrera, Margarita Palau, Victor Moreno, Carlo La Vecchia, Gabriella Aggazzotti, Mark J Nieuwenhuijsen, and Manolis Kogevinas

Table of Contents

Table S1. Previous studies evaluating colorectal cancer from individual-based studies (case-control or cohort designs) including incident cases with exposure assessment based on personal information from residential histories

Table S2. Single nucleotide polymorphisms (SNPs) of *CYP2E1* and *GSTZ1* examined in the Spanish population of the study, and interaction p-value for total trihalomethanes (THM), chloroform (CHCl₃), and brominated THMs (BrTHM) dichotomized at the percentile 75, that are respectively 60, 20 and 40 µg/l.

Figure S1. Distribution of exposure density of average lifetime THM concentrations in residential tap water ($\mu\text{g/l}$) among 1837 cases and 3488 controls with exposure estimates $\geq 70\%$ of the exposure window. Note that scale of x- and y-axes differ by area.

Figure S2. Exposure-response relationship between residential trihalomethane (THM) levels (X axis, in $\mu\text{g/l}$) and colorectal cancer risk (Y axis, expressed in odds ratios) among 1837 cases and 3454 controls. Odds ratios (95 CI) are adjusted for sex, age, area, education, smoking, physical activity, non-steroidal anti inflammatory drugs and family history of colorectal cancer. Excludes unsatisfactory questionnaires and subjects with THM estimated less than 70% from the exposure window. Tick marks above the x-axes represent observations, and the dashed lines represent the 95% confidence intervals.

Figure S3. Spline of colorectal cancer risk (odds ratio, Y axis) associated with chloroform levels ($\mu\text{g/l}$, X axis) among men, from generalized additive models adjusted for age, sex, education, smoking, non-steroidal anti inflammatory drugs, smoking, physical activity and family history of colorectal cancer. P-value of gain from the linearity is statistically significant in Barcelona (p-value <0.001), Leon (p-value 0.03), Madrid (p-value 0.04), and Navarra (p-value 0.01). Tick marks above the x-axes represent observations, and the dashed lines represent the 95% confidence intervals. Note that scale of x -axes differ by area.

Figure S4. Spline of colorectal cancer risk (odds ratio, Y axis) associated with total brominated THM levels ($\mu\text{g/l}$, X axis) among men, from generalized additive models adjusted for age, sex, education, smoking, non-steroidal anti inflammatory drugs, smoking, physical activity and family history of colorectal cancer. P-value of gain from the linearity is statistically significant in Barcelona (p-value <0.001), Cantabria (p-value <0.01), and Navarra (p-value <0.01). Tick marks above the x-axes represent observations, and the dashed lines represent the 95% confidence intervals. Note that scale of x-axes differ by area.

Figure S5. Exposure-response relationship between ingested THM levels (X axis) and colorectal cancer (Y axis, expressed in odds ratios (OR) with 95% confidence intervals (95% CI)) among 2047 cases and 3684 controls. Adjusted for sex, age, area, education, smoking, physical activity, non-steroidal anti inflammatory drugs, and family history of cancer. Excludes unsatisfactory interviews and subjects with less than 70% THM estimated from the exposure window. P-value gain compared to linearity is <0.01 for all models, except for chloroform in women (p-value=0.32). Tick marks above the x-axes represent observations, and the dashed lines represent the 95% confidence intervals. Note that scale of x-axes differ by area.

Figure S6. Exposure-response relationship between shower-bath THM levels (X axis) and colorectal cancer risk (Y axis, expressed in odds ratios (OR) with 95% confidence intervals (95% CI)) among 1702 cases and 3269 controls. Adjusted for (sex), age, geographical area, education, non steroidal anti inflammatory drugs consumption, smoking, physical activity and family history of colorectal cancer Tick marks above the x-axes represent observations, and the dashed lines represent the 95% confidence intervals. Note that scale of x-axes differ by area.

Table S3. Association between colorectal cancer and average THM concentrations in residential tap water by cancer site among 1273 colon cases, 537 rectal cases, and 3454 controls (27 cases had an unspecified localization).